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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,067	WEINER ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-11 and 13-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-11 and 13-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0-0

DETAILED ACTION

Applicant's response and amendments of 2/15/05 have been entered.

Claim 12 is cancelled.

Claims 5-8, 17, and 33 are cancelled.

Claims 1-2, 5-11, and 13-34 are pending and considered.

New Examiner Assignment

The Examiner assigned to this case has changed. The new Examiner is Examiner Robert M. Kelly, of Art Unit 1632, TC 1600. Future correspondence should be addressed accordingly.

Withdrawal of Finality

Because Applicant's amendments bring some of the claims into the scope previously considered allowable by the Examiner, finality of the rejection and the following action is a non-final rejection.

Claim Rejections - 35 USC § 112 – indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's argument and amendments and claim cancellations, the rejections of claims 9-17 under 35 USC 112, second paragraph, for being indefinite, are alternatively withdrawn, or rendered moot, and thus are withdrawn.

Claim Rejections – 35 USC 112, first paragraph – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's amendments and arguments, and claim cancellations, the rejections of claims 6-8, 12, 17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are alternatively withdrawn, or rendered moot, and thus are withdrawn.

Claims 1-2, 6-11, 14-16, 18-24, and 29-30 remain rejected, and claims 32 and 34 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons set forth in the prior Official Actions. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For the sake of clarity, the Examiner reiterates the rejection below.

Claims 1-2, 6-11, 14-16, 18-24, and 29-30 encompass any macrophage-specific promoter, and further limit these promoter to being derived from a human gene (claim 25 and dependent claims).

The specification defines the term "macrophage-specific promoter and/or promoter specific for cells of macrophage lineage" as "a promoter that encodes a protein endogenously produced exclusively by macrophage cells and/or cells of macrophage derived lineage." (SPECIFICATION, p. 9, paragraph 2). The Examiner interprets this definition to mean that macrophage-specific promoters encompass "a promoter that is, in nature, operatively linked to a sequence encoding a protein that is produced exclusively by macrophage cells." And that a

promoter for cells of macrophage lineage to encompass the parallel promoters that are operatively linked in nature to a sequence encoding a protein that is produced exclusively by cells of a macrophage-derived lineage (i.e., cell that are formed the differentiation of a macrophage). A few examples provided are the promoters of a catalase, a CD156, a M-CSFR, a p73, and a FcgR gene (Id.).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, a few promoters are disclosed, or to be more specific, the genes in which the promoters are found (SPECIFICATION, p. 9, paragraph 2). However, the specification does not provide any disclosure as to what would have been the required structure which would promote specific expression of an operably linked sequence in a macrophage-specific (i.e., exclusive to macrophage) manner, even if limited to promoters derived from human genes. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are the functional characteristics discussed above (exclusive production of the operably linked protein found in nature, in macrophages).

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds

of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any macrophage-specific promoter, even those found in human genes, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Response to Argument – Written Description

Applicant's arguments of 2/15/05 have been fully considered but are not found persuasive.

Applicant argues that that genera of macrophage-specific promoter is demonstrated by an adequate number of species, i.e., the five specifically-disclosed species addressed in this Official Action, above (Applicant's argument of 2/15/05, pp. 11-12).

Such is not persuasive. The demonstration of possession by an adequate number is one that the Artisan could use to determine that Applicant possessed the claimed genera. In the instant case, the only manner in which the Examiner can determine such possession by an adequate number of species is the determination of some relevant identifying structure related by cause-and-effect to the promotion, exclusively, in macrophage cells (above). Moreover, as has been stated, such disclosure of five species does not the Examiner to make such a determination, as these promoters have different structures, and as such, must respond to different stimuli. Hence, the structure of a macrophage-specific promoter is simply provided by Applicant in terms of a functionality, and not such representative structure can be determined. Lastly, no other form of reasoning is apparent to the Examiner such that the broad genera of macrophage-specific

promoter can be determined by the Examiner. These arguments have been provided throughout the prosecution history by Examiner Shukla (e.g., Official Action of 12/15/04, pp. 2-3).

Applicant argues that the conclusory remark provided by Dr. Weiner's declaration of should not be dismissed by the Examiner and demonstrates that Applicant had possession of the claimed genera at the time of filing (Applicant's argument of 2/15/05, p. 13).

Such is not persuasive. Dr. Weiner has not provided any specific reasoning as to why the genre of macrophage-specific promoter would be determined to be possessed, such the Examiner would be able to remove the rejection. As stated previously, such conclusory remarks, without evidence or reasoning, do not overcome the rejection (Official Action of 12/15/04, pp. 2-3).

Applicant argues that Dr. Weiner's declaration is not a conclusory statement, but instead a factual statement, and as such the Artisan would know that the macrophage specific promoter would encompass a nucleotide sequence, and be macrophage specific (Applicant's argument of 2/15/05, pp. 13-14).

Such is not persuasive. Dr. Weiner's statement is an opinion, because it is not supported by evidence or other scientific reasoning to demonstrate possession.

Applicant argues that the specific core structure is not required, that they are not required to provide anything more than "sufficient detail" to demonstrate possession, and that they are not claiming the promoters, per se, but instead the promoter in the context of a vector used in various protocols. As such, Applicant argues that they have demonstrated possession of the genera (Applicant's argument of 2/15/05, pp. 14-15).

Such is not persuasive. First, as has been stated above, while Applicant is not required to provide any core structure, such core structure is the only line of reasoning, linked with function,

to determine possession, that the Examiner has found: if Applicant has another line of reasoning to demonstrate possession, they are requested to provide such reasoning. Second, sufficient detail, to determine possession, naturally encompasses such core structure, or other reasoning to demonstrate such possession, which Applicant has not yet provided. Lastly, with regard to the fact that the promoters are not claimed *per se*, they are nonetheless claimed and therefore required to meet the requirements of 35 USC 112, first paragraph. Hence, Applicant has not provided adequate written description to demonstrate possession of the genera claimed.

35 USC 112, first paragraph – Enablement

In light of Applicant's amendments, arguments and claims cancellations, the rejection of claims 1-2, 5-8, and 32-33 under 35 U.S.C. 112, first paragraph, because the specification does not provide an enabling disclosure for the fully-claimed scope of the claims, is withdrawn or alternatively rendered moot, and thus withdrawn.

In light of Applicant's amendments, arguments and claims cancellations, the rejection of claims 9-22 under 35 U.S.C. 112, first paragraph, because the specification does not provide an enabling disclosure, is withdrawn or alternatively rendered moot, and thus withdrawn.

Claim 1-2, 5-11, 13-17, 29, and 32-34 remain and/or are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method of delivering a protein to a macrophage cell of an individual, comprising:

Administering to said individual at a site on said individual's body, a DNA vector comprising a sequence encoding said protein, operably linked to a promoter selected from the

group consisting of a CD156 promoter, a M-CSFR promoter, and a Fc-gamma-RI promoter, and a polyadenylation signal that is functional in a macrophage cell, wherein said DNA vector is taken up by a macrophage cell and said sequence is expressed to produce said protein in said macrophage cell;

(2) A method of delivering a protein to a macrophage cell of an individual, comprising:

administering to said individual by intramuscular injection, a DNA vector comprising a nucleotide sequence that encodes said protein, wherein said DNA molecule is operably linked to a macrophage-specific promoter and a polyadenylation signal that is functional in a macrophage cell, wherein said promoter is selected from the group consisting of a CD156 promoter, a M-CSFR promoter, and a Fc-gamma-RI promoter, wherein said DNA molecule is taken up by a macrophage cell and said sequence is expressed to produce said protein in said macrophage cell;

(3) A method of delivering a protein to a lymphnode of an individual, comprising:

indentifying the lymphnode to which protein is to be delivered;

locating a site proximal to said lymphnode;

administering to said individual at said site, a DNA vector comprising a nucleotide a sequence encoding said protein, operably linked to a secretion signal, promoter selected from the group consisting of a CD156 promoter, a M-CSFR promoter, and a Fc-gamma-RI promoter, and a polyadenylation signal that is functional in a macrophage cell,

wherein said DNA vector is taken up by a macrophage cell proximal to said lymphnode, the nucleotide sequence is expressed in such macrophage, and said macrophage drains to said lymphnode, thereby delivering the protein to said lymphnode;

(4) A method of delivering a desired protein to an individual, comprising:

administering to said individual a DNA vector comprising a nucleotide sequence that encodes said protein, operably linked to a promoter selected from the group consisting of a CD156 promoter, a M-CSFR promoter, and a Fc-gamma-RI promoter, and a polyadenylation signal that is functional in a macrophage cell, wherein said DNA vector is taken up by a macrophage cell and expressed to produce said protein in said macrophage cell,

does not reasonably provide enablement for any macrophage-derived lineage, any type of DNA molecule, any macrophage-specific promoter derived from a human gene, a catalase promoter, a p73 promoter, the delivery of proteins to the lymphnode where the protein is not linked to a secretion signal, or the delivery of proteins to a lymphnode not proximal to the site of injection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 18-28 and 30-31 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Background

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple

factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

The Breadth of the Claims

Applicant's claims encompass various aspects of large breadth which are not enabled, or not enabled for their fully-claimed breadth. Specifically, Applicant's claims encompass any cell derived from a macrophage, any type of DNA molecule for gene transformation, any macrophage specific promoter, which promoter may be derived from any human gene, the lack of secretion signals in delivering proteins the lymphnode via transformation of a macrophage, promoters of catalase, promoters of p73, inducing an immune response via transgene expression

of proteins in macrophages, and eliminating cells in a lymphnode via transgene expression of toxins in macrophages.

Because of the breadth of these aspects, and the fact, as shown below, that the art has corresponding issues that lack reasonable predictability, the Artisan would have had to perform undue experimentation to determine the working embodiments, and to do so for the fully-claimed scope of Applicant's invention.

The Nature of the Invention and State of the Art

Applicant's invention is in the nature of gene therapy. Gene therapy, however, is not generally enabling of new inventions in the field.

To, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is

gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing to reasonably predict that

enough nucleic acid reaches the target cells (*in vivo*) and/or enough transformed cells reach the target sites and survive (*ex vivo* and drainage to lymphnodes), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, and the protein is properly trafficked to its site of action (e.g., delivery to the lymphnode), to effect treatment, and that such occurs for a long enough period of time to effect treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, encoding specific proteins, under the control of specific promoters and other control elements, would overcome this showing for that specific method of administration to that specific species, because, if treatment is successful, it must have met these aforementioned requirements.

With regard to Applicant's claiming of any cell derived from a macrophage, macrophages are terminally differentiated, and as such, Applicant is claiming a non-extant genera of cells. To wit, U.S. Patent Application Publication No. 2004/0224404 states that macrophages are terminally differentiated, do not undergo cellular division, and are not readily transduced with commonly used vectors (p. 2, paragraph 0007). Hence, there are no cells of macrophage-derived linage or promoters active in such non-extant cells.

Moreover, from the quoted paragraph, and from the previous analysis of vectors above (i.e., that transformation is transient in cells), it is clear that DNA vectors, which do not integrate, would be even less predicted to express any protein for a long enough period of time to effect any desired effect. Further, if such DNA molecule is not a double-stranded plasmid DNA, it would not be predicted to transcribe any gene, as this form of DNA is required for transcription,

otherwise the DNA would not be transcribed, or would be degraded before any transcription could take place.

With regard to any promoter that is macrophage specific and derived from any human gene, such promoter structure required to effect macrophage-specific transcription is not reasonably predictable. The art simply does not address how any specific promoter may be modified to make it specific for any other specific cell type. Hence, the Artisan would not be able to reasonably predict which modifications to make to any particular promoter to make such promoter macrophage-specific.

With regard to the delivery of proteins to a lymphnode via macrophage transformation, such proteins are required to have a secretion signal, otherwise the protein would remain within the macrophage, and not be delivered to the lymphnode at all, they would simply within a macrophage that is, for a time, within a lymphnode. Therefore, without a secretion signal, the Artisan would not reasonably predict that such protein would be delivered to the lymphnode.

With regard to the promoters of catalase and p73, while Applicant claims that these genes encode promoters specific for macrophages, the Examiner has failed to find any art that teaches or suggests that such genes are specifically expressed in macrophages. To wit, Applicant's specification states that "As used herein the term 'macrophage-specific promoter and/or promoter specific for cells of macrophage derived lineage' is meant to refer to a promoter that encodes a protein endogenously produced exclusively by macrophage cells and/or cells of macrophage derived lineage." (p. 9, paragraph 2). While the Examiner assume that Applicant has simply mistyped that the promoters encode proteins, the specific examples of such promoters given include catalase and p73. Catalase, from the Examiner's search of the art, is a protein that

is widely expressed in many organisms, and is associated with macrophages in the protection of prokaryotes from macrophages during infection (e.g., Adak, et al. (2005) Biochem J., manuscript BJ20050311), and is found to be expressed in mammalian tissues other than macrophages, e.g., liver, and is associated with response to peroxidases in general (e.g., Deyulia, et al, (2005) Proc. Natl. Acad. Sci., USA., 102(14): 5044-49, ABSTRACT; Id., p. 5045, col. 1, paragraph 6, "bovine liver catalase"). Hence, the Artisan would not reasonably predict that any particular catalase promoter is specific for expression in human macrophages. With regard to p73, Kikuchi, et al. (2004) Int. Immunol., 16(6): 831-41, demonstrates that p73 is expressed in thymic epithelial cells, and may thereby alter regulation of GM-CSF which may affect macrophages (ABSTRACT). Hence, the Artisan would not reasonably predict that the p73 promoter is specific for macrophages.

With regard to the elimination of cells of the lymphnode, it is not reasonably predictable that any such effect could be achieved, because the use of toxins would be predicted to kill the cell producing the toxin before any such effect could be achieved. For example, one of Applicant's claimed toxins is ricin. Ricin blocks the activity of ribosomes, which are required for protein translation. (Marsden, et al. (2005) Expert Rev. Vaccines, 4(2): 229-37, p. 229.) Hence, if a macrophage expresses Ricin, it is reasonably predictable that the ribosomes of such macrophage will be blocked, and thereby block further transcription, thereby killing the macrophage before any protein could be delivered to the lymphnode. Another claimed toxin is diphtheria toxin. Similar to Ricin, diphtheria toxin is an inhibitor of protein synthesis, and as such would not be predicted to produce enough protein before inhibiting its own protein synthesis to have any effect on other cells than the specific cells expressing such toxin (e.g., Lee,

et al. (2005) Biochimica et Biophysica Acta, 1747: 121-31, p. 121). Hence, for any particular toxin, it is not reasonably predictable that such toxin would not kill the macrophage before the macrophage could even deliver such toxin to the lymphnode to kill cells of the lymphnode. Such is why such toxins are usually used in cancer cell killing, i.e., killing the cell so-transformed (e.g., Zheng, et al. (2003) Cancer Gene Therapy, 10: 764-70, whole article). The Art simply does not recognize killing of cells other than the cell transformed. Hence, the Artisan would find that macrophages transformed with any cytotoxin-expressing gene would not be reasonably predicted to eliminate any cells of the lymphnode.

With regard to modulating the immune system of an individual, the immune system is complicated system, encompassing many cells types and biochemical processes to effect various immune responses. Therefore, in Applicant's claims encompassing the modulation of the immune system, Applicant's claims would be required to be enabled for any particular modulation within the immune system, and a reasonably predictable use for such modulation. For example, one such aspect would be the increase of CD8+ cells expressing CD28 and producing IL-2 in response to activation signals. (Roitt, et al. (1993) Immunology, 3rd Ed., by Mosby, Boston, MA., p. 2.6.) However, the full involvement and method of involvement of the gall bodies of such cells is not known, and the Art does not demonstrate how to modulate such cells via any particular trangene, particularly when expressed in macrophages only. Hence, for any particular aspect encompassed by Applicant's modulation of the immune system, it is not reasonably predictable how to effect such modulation, much less the effects of such modulation. Hence, the scope of modulation of the immune system is not reasonably predictable.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose any macrophage-derived cells or promoters active therein, the use of any type of DNA molecule for transforming cells, the use of proteins without secretion signals to deliver such protein to another cell, how to derive a macrophage-specific promoter from any human gene, that catalase and p73 promoters are specific for macrophages, any elimination of lymphnode cells via another cell, and the modulation of any particular aspect of the immune system in a reasonably predictable fashion or the use of such modulation, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Direction and Guidance provided by Applicant

Applicant's specification broadly discusses the delivery of DNA expression cassettes, and the use of such to elicit immune responses (pp 1-3), a summary of the invention roughly tracking claim language (pp. 3-5), a brief description of the drawings (pp. 5-7), the ability of

macrophages to take up DNA and produce protein, and drain to the lymphnodes (pp. 7-8), a definitions section (pp. 8-10), expression of proteins in macrophages and cells of the macrophage-derived lineage (pp. 10-11), specific methods of administration, the use of plasmids, promoters, polyA signals, administration with compositions for facilitating uptake of DNA (pp. 11-12), delivering protein to a lymphnode (pp. 12-13), inducing an immune response (pp. 13-17), treatments (pp. 17-19), immunodulatory proteins (p. 19), various definitions (p. 22), aspects of vector construction (pp. 22-23), pharmaceutical compositions (pp. 23-16).

However, such broad description does not provide the specific direction and guidance that the artisan would require to reasonably predict that enough nucleic acid reaches the target cells (*in vivo*) and/or enough transformed cells reach the target sites and survive (*ex vivo* and drainage to lymphnodes), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, and the protein is properly trafficked to its site of action (e.g., delivery to the lymphnode), to achieve any desired effect, and that such occurs for a long enough period of time to achieve such effect. Moreover, it does not provide the specific guidance and direction required of the Artisan to reasonably predict whether any cells of macrophage-derived lineage exist, or promoters active therein, whether any form of DNA could be used for transcription, how to make a macrophage specific promoter from any human promoter, how to deliver proteins to the lymphnode without a secretion signal, whether catalase promoters and p73 promoters are macrophage-specific, whether cytotoxins would kill the macrophage before delivery to the lymphnode, thereby precluding delivery, or how to modulate any specific aspect of the immune system, much less the use of such modulation.

Applicant's Examples

Applicant's first example demonstrates the construction of plasmids encoding various proteins under the control of the CMV-IE promoter. When such plasmids were injected, intramuscularly, into mice, protein was expressed, including in macrophages, and induced immune responses, and altered various aspects of the immune system, and the protein was expressed in such macrophages which had drained to a lymphnode proximal to the site of injection. Moreover, Applicant admits that the understanding of the immune system is incomplete (p. 35, paragraph 2).

As such Applicant has demonstrated that macrophages express such proteins, as well as other cells local to the site of injection (Example 1). Moreover, Applicant has demonstrated that the macrophage may express the protein and drain to the lymphnode.

Example 2 demonstrates similar immune response in animals wherein the CD3 promoter (another non-macrophage specific promoter) drives immune response to nef in similar tests in mice.

However, these examples do not provide the information required of the Artisan to reasonably predict that enough nucleic acid reaches the target cells (*in vivo*) and/or enough transformed cells reach the target sites and survive (*ex vivo* and drainage to lymphnodes), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, and the protein is properly trafficked to its site of action (e.g., delivery to the lymphnode), to achieve any desired effect, and that such occurs for a long enough period of time to achieve such effect. Moreover, it does not provide the information required of the Artisan to reasonably predict whether any cells of macrophage-derived lineage

exist, or promoters active therein, whether any form of DNA could be used for transcription, how to make a macrophage specific promoter from any human promoter, how to deliver proteins to the lymphnode without a secretion signal, whether catalase promoters and p73 promoters are macrophage-specific, whether cytotoxins would kill the macrophage before delivery to the lymphnode, thereby precluding delivery, or how to modulate any specific aspect of the immune system, much less the use of such modulation.

Lastly, Applicant's examples are not using macrophage-specific promoters, and therefore, it is not clear whether such immune system responses are derived from the expression in other cells types, or whether the macrophage is mounting such immune responses. Hence, Applicant's invention is not reasonably predicted, from the art and information given, to produce any immune response due to macrophage-specific expression of any particular protein.

Undue Experimentation

Because of the lack of reasonable predictability, the Artisan would be required to perform undue experimentation to determine whether enough nucleic acid reaches the target cells (*in vivo*) and/or enough transformed cells reach the target sites and survive (*ex vivo* and drainage to lymphnodes), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, and the protein is properly trafficked to its site of action (e.g., delivery to the lymphnode), to achieve any desired effect, and that such occurs for a long enough period of time to achieve such effect. Moreover, undue experimentation would be required of the Artisan to reasonably predict whether any cells of macrophage-derived lineage exist, or promoters active therein, whether any form of DNA could be used for transcription, how to make a macrophage specific promoter from any human

promoter, how to deliver proteins to the lymphnode without a secretion signal, whether catalase promoters and p73 promoters are macrophage-specific, whether cytotoxins would kill the macrophage before delivery to the lymphnode, thereby precluding delivery, or how to modulate any specific aspect of the immune system, much less the use of such modulation. Lastly, undue experimentation would be required for the Artisan to reasonably predict whether such immune responses are due to macrophage-specific expression or due to expression in other cell types.

Lack of Enablement

Because of the lack of reasonable predictability, which would require the Artisan to perform undue experimentation to find the working embodiments, such undue experimentation renders the claimed invention not enabled for its fully claimed scope, and some claims are not enabled whatsoever. Applicant should refer to the initial paragraphs for the scope of what is found enabled, and remember that although the Examiner has attempted to avoid problems with other issues, Applicant's copying of the Examiner's scope considered enabled may lead to other issues, including new matter.

Response to Argument – Enablement

Applicant's arguments have been considered but are not found relevant in light of the new reasoning provided above.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 29, and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication No. 2004/0063652 to Jolly, filed 3/29/01, and claiming priority to at least 11/25/97.

With regard to claim 1 and 29, Jolly teaches the coadministration of multiple vectors encoding complimentary transgenes, to effect complimentary therapies (paragraphs 002-0019). Such vectors may be DNA plasmids (paragraph 0037). One such therapy is to express the thymidine kinase gene of HSV in macrophage cells (paragraphs 0067-0071) and may be made more specific by expression under macrophage-specific promoters (paragraph 0068), wherein the invention is to include a second transgene with a second cytotoxic activity, e.g., ricin (paragraph 0065). Furthermore, the promoter may be a human promoter with macrophage-specific expression, as the publication teaches the use of human promoters (e.g., paragraph 0048) and the fact that the such promoters would inherently be used to effect treatment of humans (e.g., paragraph 003). Hence, at the time of invention by Jolly, it was already known to express HSV-tk in macrophage cells, and Jolly teaches the use of such macrophage specific promoters. Moreover, Jolly teaches that such macrophage cells can be transformed *in vivo* (paragraph 0071), resulting in greater efficacy, delivery of lower doses, less generalized toxicity, and higher potency against productive infection (paragraph 0068). Such results in selective killing of such macrophage cells when exposed to a prodrug (paragraph 0071).

With regard to claim 2 and 32, Jolly teaches, *inter alia*, intramuscular administration (paragraph 0171).

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7-8, 17, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2004/0063652 to Jolly, filed 3/29/01, and claiming priority to at least 11/25/97 and Kataoka, et al. (1997) J. Biol. Chem., 272(29): 18209-15.

Jolly, in addition to teaching the use of plasmids encoding HSV-tk (see 35 USC 102(e) rejection, above), also teaches the administration of blocking proteins to block pathogenic interactions, which may be in secretable form (paragraph 0155) to block pathogenic interactions local to the cell (Id.). Hence, Jolly is inherently teaching the use of secretion signals, as such is the mechanism in which proteins are secreted. Moreover, such compositions may be administered with bupivacaine, which helps with the transfection of the cells (paragraph 0365). However, Jolly does not teach the specific promoters claimed.

On the other hand, Kataoka teaches the human CD156 gene, and its promoter sequence as specific for macrophage expression, as well as the structure of such promoters (p. 18215).

Therefore, at the time of invention by Applicant, it would have been obvious to modify the invention of Jolly, by using the CD156 human gene promoter. The Artisan would have been

motivated to do so because the CD156 promoter is specific for macrophages of humans, as is taught to be desired by Jolly. Moreover, the Artisan would have had a reasonable expectation of success, as Jolly had already demonstrated the methods, and Kataoka had demonstrated that the CD156 promoter is specific for macrophages.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2004/0063652 to Jolly, filed 3/29/01, and claiming priority to at least 11/25/97 and Kataoka, et al. (1997) J. Biol. Chem., 272(29): 18209-15 as applied to claim 5 above, and further in view of U.S. Patent No. 5,763,416 to Bonadio, et al., filed 2/18/94 and Patented 6/9/98.

As shown above, the Jolly reference and Kataoka reference obviate the base claim, claim 5, however they do not teach or suggest the use of the SV40 polyA signal.

On the other hand, Bonadio teaches that the SV40 polyA signal is a standard polyA signal for termination of transcripts (e.g., EXAMPLE IX).

Hence, at the time of invention by Applicant, it would have been obvious the methods of Jolly and Kataoka with the polyA signal as taught by Bonadio. The Artisan would have been motivated to do so because such promoter was known in the art to terminate transcription. Moreover, the Artisan would have had a reasonable expectation of success, as Bonadio had previously shown such polyA sequence to be able to terminate transcription, confirming what was well known in the Art.

Note to Applicant

Should Applicant overcome the rejections based on lack of enablement for inducing an immune response, for modulating the immune system, and for eliminating cells of the lymphnode, Applicant should note that rejections based on U.S. Patent Application Publication No. 2004/0063652 may be subsequently applied, as this reference does describe the use of vectors for inducing immune responses with genes driven by macrophage-specific promoters, as discussed in the art rejections above. Moreover, the Examiner, in light of U.S. Patent No. 5,783,567, which teaches that the macrophages drain into the lymphnodes (col. 8, paragraph 3), considers this aspect inherent in the methods of Jolly. However, the Examiner has failed to find any art of record that would indicate the targeting of specific lymphnodes local to a site of administration for delivery of proteins by macrophages.

CONCLUSION

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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